Organerhalt bei Larynx/Hypopharynxkarzinomen: Ergebnisse der DELOS II Studie

Andreas Dietz, Gunnar Wichmann on behalf of the DeLOS-Study-Group
principles in therapy
Head and Neck

- **Resectable**
  - Organ preserving surgery
  - Adjuvant radio-, radiochemo-therapy
  - Organ preserving chemo-radiation

- **Non-resectable**
  - Ablative surgery
  - Chemo-radiation
Summary intro

- Since publication of EORTC 24891\(^1\) and VA\(^2\) trials for non-surgical organ preservation in advanced laryngeal and hypopharyngeal cancer, there has been debate on the most suitable protocol for balancing survival without laryngectomy with acceptable late toxicity and functional outcome\(^3\).

- Following publication of the 10-year results of the RTOG 91-11 trial in 2013,\(^1\) concurrent platin-based CRT continues to be recommended in the USA; however, concurrent CRT showed a significantly higher rate of non-cancer-related deaths compared with other arms\(^1\).

- The GORTEC 2000-01 trial demonstrated acceptable feasibility and efficacy of TPF ICT in larynx organ preservation\(^4\).

- The DeLOS I trial demonstrated acceptable feasibility and efficacy of TP induction with encouraging low rates of late dysphagia after 3 years\(^5\).

- Addressing the high toxicity of TPF, Argiris et al. introduced TPE induction in advanced head and neck cancer at ASCO in 2008\(^6\).

Induction chemotherapy (IC) docetaxel (T), cisplatin (P), 5-fluorouracil (F) (TPF) or TP followed by concomitant boost radiotherapy (R) with or without cetuximab (E) for functional organ preservation (FOP) of resectable laryngeal and hypopharyngeal cancer (LHSCC): first results of the phase II randomized DeLOS-II study.


Presented by: Andreas Dietz; selected for poster highlights session

TP both 75 mg/m² day 1 and F 750 mg/m²/day on days 1–5 without (arm A) or with (arm B) standard dose of cetuximab for 16 weeks. RT: concomitant boost radiotherapy (69.6 Gy)

TPF

T 75 mg/m² d1
P 75 mg/m² d1
F 750 mg/m² d1–5

Cetuximab

400 mg/m² d 1, then 250 mg/m² q1w


A

1 cycle

TP

PR

yes

Surgery

2 cycles

TP

PR

yes

no

B

TP + cetuximab

PR

no

Surgery

TP + cetuximab

RT

RT + cetuximab

TP

Cetuximab

T 75 mg/m² d1

400 mg/m² d1, then 250 mg/m² q1w

P 75 mg/m² d1

TP both 75 mg/m² day 1 on days 1–5 without (arm A) or with (arm B) standard dose of cetuximab for 16 weeks. RT: concomitant boost radiotherapy (69.6Gy)

DeLOS II methods: Integrating selection due to endoscopic response evaluation

Case of T4 supraglottic laryngeal cancer infiltrating hypopharyngeal structures

Videoendoscopic response evaluation two weeks after first cycle of ICT

Inclusion criteria:
Endoscopic evaluation of surface shrinkage after first cycle: Minimum 30%*

(*empiric cut off; not related to RECIST)

DeLOS II: Early response rate

- Early response rate: complete study population n=174  
  (response defined as 30% surface shrinkage in endoscopy after first cycle)

<table>
<thead>
<tr>
<th>Group</th>
<th>n (%)</th>
<th>p-value*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPF/TP, n=86</td>
<td>58 (67.4)</td>
<td>0.1469</td>
<td>56.5–77.2</td>
</tr>
<tr>
<td>TPF/TP + cetuximab, n=88</td>
<td>68 (77.3)</td>
<td></td>
<td>67.1–85.5</td>
</tr>
</tbody>
</table>

One early responder had not marked if CR or PR and is counted as PR

* Chi-square test (2-sided alpha = 0.05)

DeLOS II: Overall response rate after finishing therapy

- Subgroup: Early responder (n=126)

<table>
<thead>
<tr>
<th>Response</th>
<th>TPF/TP n (%)</th>
<th>TPF/TP + cetuximab n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>47 (81.0)</td>
<td>53 (77.9)</td>
<td>100 (79.4)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (8.6)</td>
<td>4 (5.9)</td>
<td>9 (7.1)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (1.7)</td>
<td>1 (1.5)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>PD</td>
<td>–</td>
<td>2 (2.9)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>NE</td>
<td>4 (6.9)</td>
<td>4 (5.9)</td>
<td>8 (6.3)</td>
</tr>
<tr>
<td>NE (death before restaging)</td>
<td>1 (1.7)</td>
<td>2 (2.9)</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>NE (termination of study treatment before restaging)</td>
<td>–</td>
<td>2 (2.9)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Total</td>
<td>58 (100.0)</td>
<td>68 (100.0)</td>
<td>126 (100.0)</td>
</tr>
</tbody>
</table>

Overall response is the result of restaging at final assessment

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated

DeLOS II: Survival with a functional larynx (6 months) – Kaplan Meier analyses

ITT population, n=174

<table>
<thead>
<tr>
<th></th>
<th>Min¹</th>
<th>Max¹</th>
<th>HR</th>
<th>95% CI (HR)</th>
<th>p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPF / TP, n=86</td>
<td>0.4</td>
<td>5.9</td>
<td>0.502</td>
<td>0.267 –0.944</td>
<td>0.0289</td>
</tr>
<tr>
<td>TPF / TP + cetuximab, n=88</td>
<td>0.5</td>
<td>5.5</td>
<td>0.502</td>
<td>0.267 –0.944</td>
<td>0.0289</td>
</tr>
</tbody>
</table>

¹ Patients, who reached the endpoint (loss of functional larynx due to laryngectomy, recurrent disease, tumor progression, death).
² Log-rank test (2-sided, alpha = 0.05).

Endpoint (loss of FOP, death) was reached in 31.4% vs. 17.0%, favoring TPF/E/TPE

DeLOS II: Predictive value of early response

- High predictive value of early response after one cycle and overall response after end of complete treatment within the subgroup of early responders (n=116)

<table>
<thead>
<tr>
<th>Early responder</th>
<th>TPF/TP, n=54</th>
<th>TPF/TP + cetuximab, n=62</th>
<th>Total, n=116</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Late responder*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (3.7)</td>
<td>52 (96.3)</td>
<td>5 (8.1)</td>
</tr>
<tr>
<td>Late responder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CR and PR at final assessment

...radiomic signature, capturing intratumour heterogeneity, was strongly prognostic and validated in three independent data sets of lung and head-and-neck cancer patients, and associated with gene-expression profiles.
Response judged by clinical inspection, surface reduction ≥30% as criterion

Leipzig DeLOS-subgroup: Responder: n=32, Nonresponder: n=9
Volume assessed by 3-D-segmentation (non RECIST)
♂ 64 Jahre
Hypopharynx-Ca,
ED 09/14
(DeLOS-II-Protokoll)

20.09.2014

29.10.2014
After 1 cycle TPE
18F-FDG-PET/MRT Staging
25.09.2014

Prof. Regine Kluge; Dr. Sandra Purz; Klinik und Poliklinik für Nuklearmedizin, Universität Leipzig, Direktor: Univ.-Prof. Dr. med. Osama Sabri

MRT, T2

MRT, T1_KM

18F-FDG-PET/MRT

18F-FDG-PET

Rot = Tumor
Blau = physiologische Larynxaktivität
Restaging 28.10.2014 after 1 cycle chemotherapy (DeLOS-II-Protokoll)

18F-FDG-PET/MRT
red = residual tumor
blue = normal Larynx activity
18F-FDG-PET/MRT
Staging
25.09.2014

Reduction of metabolic activity > 80%

Restaging 28.10.2014
after 1 cycle chemotherapy (DeLOS-II-Protokoll)
Responders: high correlation ($r>0.8$) in volume assessed by segmentation and metabolic volume in $^{18}$FDG-PET
Gunnar Wichmann, Maciej Rosolowski, Knut Krohn, Markus Kreuz, Andreas Boehm, Anett Reiche, Ulrike Scharrer, Dirk Halama, Julia Bertolini, Ulrike Bauer, Dana Holzinger, Michael Pawlita, Jochen Hess, Christoph Engel, Dirk Hasenclever, Markus Scholz, Peter Ahnert, Holger Kirsten, Mathias Hofer, Milos Fischer, Christian Mozet, Alexander Hemprich, Christian Wittekind, Oll Herbarth, Attila Tarnok, Friedemann Horn, Andreas Dietz, Markus Loeffler, Florian Lordick, Achim Aigner, Ingo Bechmann

for the Leipzig Head and Neck Cancer Study Group (LHNCSG)
FLAVINO-Assay

- Flavin protecting conditions
- Differentiation Tumor/Stroma
- Results can be quantified
- Combined activity Chemotherapy Radiation

Mozet C. et al. AAO-HNSF, 2011
Dietz A. et al. European Archives ORL, 2010
Dietz A. et al. ASCO, 2010
Dietz A. et al. European Archives ORL, 2010
Wichmann G. et al., Onkologie, 2009
Horn I. et al, Cancer Chemotherapy and Pharmacology, 2009
Dollner R. et al. Onkologie, 2004
Microscopic evaluation after antibody-labeling and immunofluorescent staining

Colonies of HNSCC in phase contrast

Green-fluorescent epithelial cells (Cy2 stained) after pan-cytokeratin staining

Fluorescent labelling of epithelial cells allows for easy differentiation between stromal and epithelial colonies
Flavino: predictive correlation with response after therapy

Response to 275 nM docetaxel (1/2 TPL)

Colony formation [% control]

p=0.0094

Nonresponder vs. Responder

LE & PD

CR

DTX 275 nM [%]
Slice cultures from head and neck squamous cell carcinoma: a novel test system for drug susceptibility and mechanisms of resistance

M M Gerlach*,1, F Merz*1, G Wichmann2, C Kubick3, C Wittekind4, F Lordick4, A Dietz2,5 and I Bechmann1,5

1Institute of Anatomy, University Leipzig, Liebigstraße 13, Leipzig 04103, Germany; 2Clinic for Otorhinolaryngology, University Hospital Leipzig, Liebigstraße 10–14, Leipzig 04103, Germany; 3Institute of Pathology, University Hospital Leipzig, Liebigstraße 24, Leipzig 04103, Germany and 4University Cancer Center Leipzig, University Hospital Leipzig, Liebigstraße 20, Leipzig 04103, Germany

A Experimental setup

Vibratome

Tissue chopper

Tumour tissue

Agar-agar

Tumour tissue before slicing

Tumour slices cut by the tissue chopper

Slices Medium Membrane

Number of nuclei

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Control
Cisplatin 6.66 μM
Cisplatin 3.33 μM
Docetaxel 0.55 μM
Docetaxel 0.275 μM
Cetuximab 66 μg ml⁻¹

B

C

**0201712

×40

×40
Summary

- Surface reduction > 30% after one cycle is predictive for therapy response
- Flavino (Cisplatin and Docetaxel) dose not correlate with surface reduction >30%
- Flavino (Docetaxel) is predictive for therapy response
- Docetaxel seems to be more specific for prediction than cisplatin